IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AFFYMETRIX, INC., a Delaware corporation, Plaintiff/Counter-Defendant, v. **ILLUMINA, INC.**, a Delaware corporation, Defendant/Counter-Plaintiff.	Civil Action No.: 04-901 JJF **PUBLIC VERSION**

ILLUMINA, INC.'S RESPONSIVE *MARKMAN* BRIEF

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TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page

Cases

Affymetrix spends the majority of its Opening Markman Brief attacking Illumina's constructions rather than attempting to support its own. This is because there is very little, if any, intrinsic support for many of Affymetrix's constructions. The best Affymetrix can do in most instances is merely argue that there is no express disclaimer in the patent to reject its proposed construction. But this "construe the claims to cover everything in the world unless I expressly disclaimed it" approach is not the way claim construction works. The Federal Circuit sitting *en banc* in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005), confirmed the longstanding principle that claims must be construed in light of the intrinsic evidence, including the claim language itself, the specification, and the prosecution history. Affymetrix seeks to have this Court ignore the intrinsic evidence and instead adopt constructions that bear no relation to the alleged inventions set forth in the patents.

Affymetrix invented a specific way of making arrays of polymers (such as nucleic acids) on a solid surface using light-directed synthesis methods akin to those used in semiconductor manufacturing. When commercializing its arrays, Affymetrix then employed basic hybridization-based methods to detect and analyze sequences of target nucleic acids. ***This*** is what Affymetrix attempted to describe in its patents. But now, seeking to cover Illumina's products that have nothing to do with Affymetrix's technology or patents, Affymetrix proffers claim constructions that bear no resemblance to the descriptions in the patents of which they are a part.

This response will first correct Affymetrix's misapplication of the governing case law, and underscore the specific claim construction maxims that dictate the correct claim constructions in this case. Illumina will then provide a specific response to each of Affymetrix's proposed claim constructions, and summarize the intrinsic evidence that supports Illumina's constructions.

I. AFFYMETRIX IGNORES CONTROLLING FEDERAL CIRCUIT PRECEDENT IN AN EFFORT TO EXPAND IMPROPERLY THE SCOPE OF ITS CLAIMS.

In an effort to expand the scope of the asserted claims, Affymetrix improperly seeks to divorce those claims from the intrinsic record of the patents-in-suit. In so doing, Affymetrix ignores years of well-established Federal Circuit precedent in at least three respects: (1) Affymetrix ignores that claim

terms may be defined through their use in the specification; (2) Affymetrix attempts to broaden its claims beyond the description of the alleged inventions in the specification, treating what the Federal Circuit calls "the single best guide to the meaning of a disputed term" as if it were barely relevant; and (3) Affymetrix ignores that distinguishing an invention from the prior art constitutes a binding disclaimer that limits the scope of patent claims. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582-83 (Fed. Cir. 1996).

A. Affymetrix Is Wrong When It Argues That This Court Should Ignore the Specification.

Affymetrix shuns long-standing Federal Circuit precedent recognizing that a patentee may act as a lexicographer and that the specification "acts as a dictionary when it expressly defines terms used in the claims or when it defines terms by implication." *Vitronics*, 90 F.3d at 1582. Throughout its brief, Affymetrix trumpets its reliance on partial definitions while pretending that the rest of the specification does not exist. For example, in construing the term "substrate," Affymetrix adopts the first part of a glossary definition offered in the specification, then ignores the remainder of the glossary definition and denies that "substrate" is used repeatedly and consistently throughout the specification as a material whose surface supports polymer synthesis. Affymetrix also highlights dictionary definitions to the exclusion of the constructions dictated by the intrinsic evidence, a practice that was specifically rejected by the Federal Circuit in *Phillips*. *Phillips*, 415 F.3d at 1320-21. An example of this is where Affymetrix seeks to rely on a dictionary definition of "housing" while ignoring the intrinsic evidence that informs the claim construction of this term.

Recent Federal Circuit authority has reaffirmed that a patentee is "not entitled to a claim construction divorced from the context of the written description and prosecution history." *Nystrom v. Trex Co.*, 424 F.3d 1136, 1144-45 (Fed. Cir. 2005). In *Nystrom*, the Federal Circuit rejected patentee's argument that the claim term "board" could not be limited to a certain type of board because the claim language did not expressly limit the material from which the board came. *Id.* at 1142. After reviewing the term "board" in the context of the written description and prosecution history, the Court concluded

that the term "board" had to be limited to wood cut from a log because, throughout the written description, the patentee consistently used the term "board" to describe wooden material cut from a log. *Id.* at 1144-45 (looking to the prosecution history for additional context consistent with the written description). The Court further reasoned that "[a]lthough there was no clear disavowal of claim scope, there was nothing in the intrinsic record to support the conclusion that a skilled artisan would have construed the term 'board' more broadly than a piece of construction material made from wood cut from a log." *Id.* at 1145.

Following *Nystrom*, this Court should reject Affymetrix's insistence on context-free constructions that ignore how the terms are defined and used in the specification. Affymetrix's position that a skilled artisan would broadly construe various disputed terms just because the specification "nowhere indicated an intent to limit" inverts the principle guarding against overbroad claiming -- the lack of any express discussion typically limits the claims to the description provided. *See, e.g., Laitram Corp. v. Morehouse Indus., Inc.*, 143 F.3d 1456, 1463 (Fed. Cir. 1998) (concluding that the disputed "driving surface" limitation requires flat driving surfaces because "nothing in the written description suggests that the driving surfaces can be anything but flat").

B. Affymetrix's Constructions Attempt To Broaden The Claim Language Far Beyond How The Alleged Inventions Are Defined And Described In The Specification.

The Federal Circuit has routinely rejected attempts by patentees such as Affymetrix to construe patent terms broadly during litigation where the express disclosure of the invention in the patent specification is narrower. For example, in *Toro*, the patentee urged a broad dictionary definition of two common terms, arguing that defendant's narrower definitions read limitations from the specification into the claims and, thus, improperly limited the claims to the preferred embodiment. *Toro Co. v. White Consol. Indus., Inc.*, 199 F.3d 1295, 1301-02 (Fed. Cir. 1999). The Court rejected patentee's argument because claims are not construed in a "lexicographic vacuum," but must be interpreted in light of the specification, including the written description of the invention. *Id.* at 1301. Illustrating the dispositive

nature of the specification, the Federal Circuit adopted a construction consistent with the only disclosed embodiment of the invention. *Id.*

Construing a claim term in light of the specification is a required part of claim construction and not, as Affymetrix contends, the same as reading limitations from the specification into the claims. *Aquatex Indus., Inc. v. Techniche Solutions*, 419 F.3d 1374, 1381-82 (Fed. Cir. 2005) (limiting disputed term "fiberfill batting material" to synthetic or polyester fiber composition because of the specification teachings, the patents incorporated by reference, and consistent industry publications). "Although the specification need not present every embodiment or permutation of the invention and the claims are not limited to the preferred embodiment of the invention, ***neither do the claims enlarge what is patented beyond what the inventor has described as the invention***." *Netword, LLC v. Centraal Corp.*, 242 F.3d 1347, 1352 (Fed. Cir. 2001) (emphasis added). Thus, the scope of the right to exclude may be limited by a narrow disclosure. *See, e.g.*, *Watts v. XL Sys., Inc.*, 232 F.3d 877, 882-83 (Fed. Cir. 2000) (limiting claim term to the structure disclosed in the specification in light of its "specific disclosure" and "limiting remarks" in the specification); *Wang Lab., Inc. v. America Online, Inc.*, 197 F.3d 1377, 1383 (Fed. Cir. 1999) (limiting "frame" to character-based frames because that was the only embodiment described in the specification); *General Am. Transp. Corp. v. Cryo-Trans, Inc.*, 93 F.3d 766, 770 (Fed. Cir. 1996) (limiting claim terms to the only described embodiment because nothing broader was suggested); *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 804 (Fed. Cir. 1999) (construing "color" to exclude black, white, and gray in light of the specification).

Throughout its brief, Affymetrix argues for various disputed terms that the claim language is broad and contains none of the limitations proposed by Illumina, despite the extensive intrinsic evidence presented by Illumina of how these alleged inventions are limited by their description in the relevant specifications and prosecution histories. Affymetrix's position is untenable given established Federal Circuit law that claim terms are limited to the invention contemplated by the patent specification, even if the language of the claims, read without reference to the specification, might be read more broadly. *See, e.g.*, *SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1341 (Fed. Cir. 2001).

Affymetrix's unsupported claim constructions are litigation-driven attempts to cover something other than what it disclosed.

C. Affymetrix Ignores Its Statements Limiting Its Claims In The Specifications And The Prosecution Histories.

Disclaimers frequently arise when an inventor distinguishes an invention from the prior art in the specification or the prosecution history because, in so doing, the applicant indicates what the claims do not cover. *See, e.g.*, *Springs Window Fashions LP v. Novo Indus., LP*, 323 F.3d 989, 994-95 (Fed. Cir. 2003); *Spectrum Int'l v. Sterilite Corp.*, 164 F.3d 1372, 1378-79 (Fed. Cir. 1998); *Cultor Corp. v. A.E. Staley Mfg. Co.*, 224 F.3d 1328, 1330-31 (Fed. Cir. 2000) (where "the inventors had repeatedly distinguished their invention from the prior art," they had explicitly limited the subject matter of their claimed invention); *O.I. Corp. v. Tekmar Co., Inc.*, 115 F.3d 1576, 1581 (Fed. Cir. 1997) (holding that "passages" were non-smooth where "the description expressly distinguishes over [smooth] prior art passages") (internal quotations omitted). A disclaimer limits the scope of patent claims because:

> The public notice function of a patent and its prosecution history requires that a patentee be held to what he declares during the prosecution of the patent. A patentee may not state during prosecution that the claims do not cover a particular device and then change position and later sue a party who makes that same device for infringement.

Springs Window Fashions LP. Thus, competitors are entitled to rely on a patentee's representations in the public record regarding the scope of the invention. *Hockerson-Halberstadt, Inc. v. Avia Group Int'l, Inc.*, 222 F.3d 951, 957 (Fed. Cir. 2000).

Affymetrix's overbroad proposed constructions run contrary to the clear statements in the specification and the prosecution histories clarifying the alleged inventions and distinguishing the prior art. The Federal Circuit has previously disapproved of Affymetrix's ostrich approach to its repeated consistent specification statements about the alleged inventions and prosecution history exchanges with the Patent Office to obtain claim allowance because "a patentee may not proffer an interpretation for the purposes of litigation that would alter the indisputable public record consisting of the claims, the

specification, and the prosecution history, and treat the claims as a nose of wax." *Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1578 (Fed. Cir. 1995).

Moreover, when multiple patents derive from the same initial application, such as the '243, '432, and '365 patents, the prosecution history for any issued patent applies to subsequently issued, related patents containing the same claim limitation. *See Elkay Mfg. Co. v. Ebco Mfg. Co.*, 192 F.3d 973, 980 (Fed. Cir. 1999). Similarly, statements made during prosecution of a later patent regarding the scope of inventions disclosed in a common specification are relevant not only to later patents, but also to earlier issued patents. *See, e.g., Microsoft Corp. v. Multi-Tech Sys., Inc.*, 357 F.3d 1340, 1350 (Fed. Cir. 2004). The touchstone is again what a reasonable competitor would understand from the remarks. *See Digital Biometrics v. Identix, Inc.*, 149 F.3d at 1335, 1347 (Fed. Cir. 1998) ("The public has a right to rely on such definitive statements made during prosecution" and noting that "[n]otice is an important function of the patent prosecution process."). In sum, Affymetrix is not entitled to a "mulligan that would erase from the prosecution history the inventor's disavowal of a particular aspect of a claim term's meaning" to achieve a strategic objective during litigation. *Hockerson*, 222 F.3d at 957.

II. THE BEAD PATENTS

A. The '243 Patent

1. "substrate"

Illumina's Construction	Affymetrix's Construction
a material having a rigid or semi-rigid surface on which polymers are synthesized	a material having a rigid or semi-rigid surface

The parties agree that a substrate is at least a material with a rigid or semi-rigid surface.[1] The dispute appears to be whether it is further defined as providing support for polymer synthesis, as proposed by Illumina. Affymetrix's argument that Illumina is attempting to read in a limitation from the specification fails in light of the intrinsic record, where Affymetrix specifically defined "substrate" with express reference to polymer synthesis, consistently described the '243 invention as a method and apparatus for synthesis of polymers on a substrate surface, and explicitly distinguished the prior art in front of the Patent Office on this basis. Affymetrix's proposed construction should be rejected for failing to incorporate the entire meaning of "substrate," as defined in the specification and confirmed in the prosecution history.

While Affymetrix admits that the '243 patent's Glossary definition of "substrate" controls, Affymetrix blindly ignores the full definition provided, which states not once but twice that the substrate surface supports polymer synthesis:

> ***A material having a rigid or semi-rigid surface***. In many embodiments, at least one surface of the substrate will be substantially flat, although in some embodiments it may be desirable to physically separate ***synthesis regions for different polymers*** with, for example, wells, raised regions, etched trenches, or the like. According to other embodiments, ***small beads may be provided on the surface which may be released upon completion of the synthesis***.

'243 col. 7:35-43 (emphasis added). This definition makes clear that polymer synthesis occurs on the "substrate" regardless of the particular embodiment. This definition further refers to the substrate and its surface in the context of "the synthesis" or "synthesis regions," showing the inventors' intent that synthesis takes place on the substrate surface regardless of substrate shape or form. Even if the referenced "many" or "other" embodiments are explanatory examples, this does not detract from the

[1] Affymetrix's attempt to accuse Illumina of shifting constructions is disingenuous and wrong. The parties established a schedule by which Affymetrix would first propose its constructions, Illumina would then provide its constructions, and the parties would then attempt to resolve the disputes before their *Markman* briefing with the Court. As it played out, Affymetrix initially provided no constructions for the '243 patent to Illumina. After providing its proposed constructions to Affymetrix, and then finally receiving the bulk of Affymetrix's constructions thereafter, Illumina proposed to incorporate Affymetrix's construction for the term "substrate" in the '243 patent within Illumina's definition, in the hope of possibly resolving the dispute. This slightly revised construction was sent to Affymetrix one business day after Affymetrix itself had sent Illumina two newly-revised constructions for other terms. Thus, Affymetrix cannot legitimately complain about the timing of Illumina's proposed constructions.

underlying requirement that polymer synthesis is performed on the intended substrate surface.[2] The entirety of the Glossary definition should be reflected in the Court's claim construction. *See, e.g.*, *Civix-DDI, LLC v. CellCo P'ship*, No. 03-C 3792, 2005 WL 831307 at *12 (N.D. Ill. Apr. 6, 2005) (adopting entire three-sentence definition in patent's specification as construction after rejecting patentee's attempt to limit construction to first sentence of definition).

Affymetrix essentially concedes that Illumina's proposed construction is correct by admitting that the glossary definition discusses embodiments where synthesis occurred on the surface of the substrate and quoting: "[a]ccording to other embodiments, small beads may be provided on the surface which may be released upon completion of the synthesis." '243 col. 7:40-43. This sentence is the ***only*** specification discussion of using beads as a support for different polymers, as required by the asserted claims of the '243 patent. As the only description of "substrate" for bead-related embodiments, the asserted claims must be construed to require the substrate surface to be the site of polymer synthesis. *See Bell Atlantic Network Servs., Inc. v. Covad Comm'ns Group, Inc.*, 262 F.3d 1258, 1273 (Fed. Cir. 2001) (limiting claim scope using inferences drawn from description of preferred embodiment because claims cannot be broadened beyond their support in the specification).

Affymetrix cannot escape the fact that the '243 patent relates to an improved method and apparatus for synthesizing a variety of chemical sequences at known locations on a substrate surface by stepwise addition of monomers using the photolithographic techniques disclosed. *See* '243 cols. 2:66-3:30; *see also* '243 Abstract; '243 cols. 3:62-65; 10:51-15:24 (Polymer Synthesis section); 29:30-31. From beginning to end, the '243 patent is replete with broad statements -- not just descriptions of specific embodiments -- that make clear the ***invention*** is the ***synthesis*** of polymers on a substrate. Setting the stage for the invention, the Background of the Invention section of the patent concludes with the following general statement:

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[2] Affymetrix's claim language argument (*see* Affymetrix', Inc.'s Claim Construction Brief [*hereinafter* "Affy. Op. Br."] at 17) is similarly ill-founded because, while the claim language does not say how the nucleic acids are synthesized, it also fails to say that the substrate must have a rigid or semi-rigid surface.

> From the above, it is seen that an improved method and apparatus for ***synthesizing a variety of chemical sequences at known locations*** is desired.

'243 col. 2:61-63 (emphasis added).[3] The Summary of the Invention then starts out with a general statement that echoes this objective:

> An improved method and apparatus for the ***preparation of a variety of polymers*** is disclosed.

Id. at col. 2:66-67 (emphasis added). The specification similarly ends with the following summary of the invention described therein:

> The present inventions provide greatly improved methods and apparatus for ***synthesis of polymers on substrates.***

Id. at col. 29:30-31 (emphasis added). These statements of general applicability confirm that Illumina's construction requiring that the substrate be the place where synthesis occurs is the correct one. *See C.R. Bard, Inc. v. U.S. Surgical Corp.*, 388 F.3d 858, 864 (Fed. Cir. 2005) (explaining that statements of general applicability, like the Summary of Invention, are especially probative to the claim construction analysis).

Affymetrix's own specification citation also supports Illumina's proposed construction. For example, Affymetrix quotes a portion of the specification discussing various materials that could serve as a substrate ('243 col. 10:54-66), but ignores the fact that this discussion is in the "Polymer Synthesis" section of the specification and the subsequent explicit statement that polymer synthesis takes place on the substrate surface:

> For example, the substrate may contain raised or depressed regions ***on which the synthesis takes place.*** The substrate and its ***surface***

[3] This statement in the Background follows a discussion distinguishing the applicants' "improved method and apparatus" for polymer synthesis on a substrate from prior art techniques for synthesizing polymers by sequential addition of monomers on various solid phase supports (*e.g.*, insoluble polymer support, reactive particles, plastic pins) by asserting that none of these prior art techniques provide an economical way to synthesize a sufficient variety of polymer sequences. *See* '243 col. 2:20-63. Because only the "improved method and apparatus" disclosed by the '243 patent allegedly solves this need for economical synthesis of a sufficient variety of polymers on a substrate surface, "substrate" must be understood in the context of the '243 patent to mean a material having a rigid or semi-rigid surface on which polymers are synthesized.

> ***preferably form a rigid support on which to carry out the reactions described herein.***

'243 col. 10:62-66 (emphasis added). The phrase "***the*** synthesis takes place" is neither exemplary nor optional, but rather confirms that polymer synthesis takes place on the substrate surface, which, according to the second sentence above, is preferably a rigid support.

Affymetrix's final argument, regarding Example H, overstates and misapplies this irrelevant experiment. As an initial matter, Example H involves attaching one pre-formed peptide to a flat slide surface and does not embody the alleged invention of the asserted claims -- it has nothing to do with nucleic acids, beads, or an array of beads with a certain density. *See* '243 col. 25:64-67. This whole discussion, therefore, has nothing to do with excluding an embodiment -- Example H is not implicated by the asserted claims at all. In any event, the '243 patent examples A-L are provided to illustrate the feasibility of the alleged "improved method and apparatus" for polymer synthesis on a substrate and detection methods ('243 col. 21:44-45) and thus progress through a series of proof-of-principle experiments towards the ultimate goal of synthesizing an array of peptides. Example H is a predicate experiment that merely establishes the known fact that "receptors to a particular polypeptide sequence would bind to a surface-bound peptide and be detected." '243 col. 25:64-67. Thus, Example H is followed by three examples (I, J, K) actually performing monomer-by-monomer synthesis of peptides using the photolithographic techniques discussed in the specification. *See* '243 cols. 26:28-27:34. The experiments culminate with the production in Example L of the desired end-product, an array consisting of a substrate upon which sixteen different amino acid sequences were synthesized, monomer-by-monomer. *See* '243 cols. 27:35-52. Only examples I through L relate to the alleged invention of polymer synthesis on a substrate described in the patent -- for Affymetrix to try to imply that Example H is an embodiment of the claimed invention merely illustrates the utter lack of intrinsic support for Affymetrix's construction.

Even if Example H somehow had some relevance to construction of the claims, Affymetrix's definition of "substrate" is still wrong because it conflicts with Affymetrix's very clear disavowal of

coverage during prosecution. As explained in Illumina's opening brief, in response to an Examiner rejection, Affymetrix distinguished a Lowe prior art reference because "Lowe *et al.* propose to attach a number of materials ***which have already been synthesized*** to a substrate . . . . ***Lowe et al. do not show or suggest synthesis of diverse compounds***." Ex. J (App. No. 07/492,462 – 3/26/97 A't at 14 (emphasis added)). In contrast to the claimed invention's "important goal" of "***synthesis*** of diverse chemical ***sequences at known locations on a substrate***," Affymetrix emphasized that Lowe "***did not propose the in situ synthesis*** of the ligand." *See id.* at 13-14 (emphasis added). By so distinguishing Lowe, Affymetrix limited the "substrate" of the alleged '243 invention to a material upon whose surface polymers are synthesized and disclaimed substrates in which pre-synthesized sequences are attached to the substrate surface. *See, e.g., Springs Window Fashions LP*, 323 F.3d at 994-96 (affirming disclaimer of claim scope based on patentee's distinguishing the prior art). Further, because the prosecution history requires Illumina's claim construction as a consequence of Affymetrix's disclaimer, it is proper to adopt this construction even if it may exclude an embodiment of the invention. *See, e.g., Rheox, Inc. v. Entact, Inc.*, 276 F.3d 1319, 1326 (Fed. Cir. 2002) (adopting claim construction dictated by the prosecution history despite exclusion of some of the preferred embodiments).

For the above reasons, as well as the additional evidence provided in Illumina's opening brief,[4] "substrate" for purposes of the '243 patent is a rigid or semi-rigid material whose surface is a support for polymer synthesis. *See Nystrom*, 424 F.3d at 1144-45 (rejecting patentee's argument that the claim could not be limited because the claim language "board" did not contain a description of the material from which the board is composed and adopting a construction limiting material of composition to reflect patentee's consistent usage of the term in the intrinsic record).

2. "target nucleic acids"

Illumina's Construction	Affymetrix's Construction
sample nucleic acids with sequence to be determined	nucleic acids that have an affinity for the nucleic acid attached to the bead

[4] *See* Illumina's Opening *Markman* Br. [*hereinafter* "Illumina Op. Br."] at 9-11.

The dispute is whether the "target" is the sample nucleic acid to be analyzed or any nucleic acid that has "an affinity" to the nucleic acid attached to the bead. Affymetrix's construction selectively adopts a sentence of the Glossary definition of "receptor" without any understanding as to how one of ordinary skill in the art would understand the term "target nucleic acids." Only Illumina's construction defines the term by its plain meaning to one of ordinary skill in the art as the sample nucleic acid sequences to be analyzed.

Affymetrix's construction adopts the definition of the term "receptor" without regard to what one of ordinary skill in the art would understand "target nucleic acids" to mean based on reading the specification. In the context of the asserted claims, one of ordinary skill in the art would understand the "target nucleic acids" to be used for the purpose of ***analyzing nucleic acid binding***, which is specified in the claim language. *See, e.g.,* '243 claim 14. This comports with the specification's discussion of analyzing nucleic acid binding ***to determine the sequence of the target nucleic acids*** through use of a substrate with known nucleic acid sequences synthesized directly on the substrate surface. '243 col. 10:3-24; *see also* Illumina Op. Br. at 14. Based on this discussion, one of ordinary skill in the art would understand that "target nucleic acids" are the nucleic acid sequences to be analyzed, and not just any generic nucleic acid with "affinity" to another sequence.

Affymetrix's construction defines the term backwards according to a general function (having an affinity for the nucleic acid attached to the bead) that essentially reads out "target" as a limitation in the claims. Under Affymetrix's construction, a "target" is ***anything that binds*** to a sequence attached to the substrate. Affy. Op. Br. at 19-20. This construction is too broad for the claimed invention because it would include as "targets" undesired sequences that bind with imperfect specificity. The specification notes that receptors can bind with varying affinities to the probes on the array. '243 col. 21:24-26 ("In practice it is found that a receptor will bind to several peptide sequences in an array, but will bind much more strongly to some sequences than others . . ."). In the context of analyzing nucleic acids, one of ordinary skill in the art understands that sequences other than the particular nucleic acid sequence to be analyzed can bind imperfectly to the probes on the array. This incomplete, mismatched binding results

from imperfectly matched based pair(s) between the probe and an undesired nucleic acid sequence. Such mismatches create inaccuracies in determining a particular nucleic acid sequence. Under Affymetrix's construction, "target nucleic acids" would include both the nucleic acid sequences to be determined as well as the unintended, mismatched sequences without distinguishing between the two, confounding the analysis. Affymetrix's construction, therefore, ignores the point of the invention and, in effect, renders the term "target" superfluous. *See Wright Med. Tech., Inc. v. Osteonics Corp.*, 122 F.3d 1440, 1444 (Fed. Cir. 1997) (rejecting construction argument that would render the limitation surplusage to cover any device with the same function); *Apple Computer, Inc. v. Articulate Sys., Inc.*, 234 F.3d 14, 25 (Fed. Cir. 2000) (rejecting construction that read the qualifier "help" out of the definition of "help access window").

Indeed, Affymetrix's construction only selectively adopts the first sentence of the definition in the specification while ignoring the rest. The Glossary describes that "receptors" are samples ***to be investigated***. '243 col. 6:45-46. Based on the Glossary definition and the examples provided, one of ordinary skill in the art would understand that "target nucleic acids" are sample nucleic acids investigated specifically to determine DNA or RNA binding sequences. '243 col. 7:5-7. The nucleic acids defined by the specification as "receptors" are clearly "target nucleic acids" because they are the nucleic acid sequences to be analyzed.

In lieu of substantive proof from the '243 patent, Affymetrix resorts to irrelevant facts and unrelated arguments. First, Affymetrix refers to the definition of "target" in other patents-in-suit, even though they are from separate families and unrelated, as Affymetrix outright admits. Affy. Op. Br. at 6. They are thus extrinsic to the construction of this term in the '243 patent and entitled to little weight. Second, Affymetrix argues that "tag" sequences are targets as used in the '432 patent when the '243 specification says nothing about such "tags."[5] Affymetrix's reliance on this unrelated patent highlights the lack of evidence supporting its overbroad construction.

[5] For the reasons stated in the '432 section, *infra*, the concept of "tag" sequences is completely unrelated to the term "target," and does not inform the claim construction issue.

All of Affymetrix's cited evidence from the specification actually confirms that one of ordinary skill in the art would understand "target nucleic acids" to be the sample nucleic acid sequences to be analyzed. The language of claim 14 makes clear that the target nucleic acids are those to be investigated. *See* Illumina Op. Br. at 13. Likewise, the specification discusses "target nucleic acids" in the context of receptors that are analyzed after binding to a substrate of known polymer sequences. '243 cols. 3:67-4:4. Further, one of ordinary skill in the art would understand that "target nucleic acids" are the sequences to be analyzed even by reading Affymetrix's specification cite regarding screening of peptides. Just as "target nucleic acids" are the molecules to be investigated in nucleic acid analysis, in screening peptides, the receptor or "target" binds with a sequence ***to obtain information about the receptor***: "To screen for biological activity, the substrate is exposed to one or more receptors . . . . Through knowledge of the sequence of the material at the location where binding is detected, it is possible ***to quickly determine which sequence binds with the receptor*** and, therefore, the technique can be used to screen large numbers of peptides." '432 col. 3:31-51 (emphasis added).

This evidence supporting Illumina's construction contrasts with the absence of any specification disclosure supporting Affymetrix's broad interpretation and confirms that one of skill in the art understands "target nucleic acids" as sample nucleic acid sequences to be investigated.

B. The '432 Patent

1. "said beads being encoded with an encoding system"

Illumina's Construction	Affymetrix's Construction
said beads having a property associated with each bead (separate from the binding polymer) that can be used to distinguish one bead from another	said beads being distinguishable one bead from another

The parties appear to agree that one bead must be distinguishable from another, but Affymetrix's proposed construction attempts to broaden the claim language and capture subject matter disclaimed during patent prosecution. The dispute before this Court is whether the intrinsic record, including the claim language and specific representations Affymetrix made to the Patent Office that an "encoding system" is a different entity than the binding polymer, requires adoption of Illumina's proposed construction.

Affymetrix explicitly represented to the Patent Office that an "encoding system" is a different entity than the binding polymer. It thus relinquished any argument that the so-called "very general" description of beads coded with an encoding system in the '432 patent specification and the claim language prove that "encoding system" must be broadly interpreted to include any means distinguishing one bead from another, including intrinsic and extrinsic encoding schemes.

Specifically, the prosecution history limits the interpretation of "said beads being encoded with an encoding system" to exclude use of a binding polymer, such as a nucleic acid, as an encoding system. As discussed in Illumina's opening brief, during prosecution of the parent application to the '432 patent at issue here, Affymetrix provided express guidance on the meaning of the term "encoding system" in a series of amendments to gain claim allowance. *See, e.g.*, *Biovail Corp. Int'l v. Andrx Pharms., Inc.*, 239 F.3d 1297, 1301-02 (Fed. Cir. 2001). Like the asserted claims here, the then-pending claims initially required a collection of substrates, "wherein different substrates bear different reagents and an encoding system." *See, e.g.*, Ex. N (App. No. 09/362,089 ("'089 App.") – 5/2/00 A't at 1 (claim 58)). In response to an examiner rejection stating that it was unclear whether each substrate bore an encoding system,

Affymetrix amended the claims to "make clear that (1) ***the reagent and tag are different entities***, (2) ***an individual bound substrate bears a tag of an encoding system*** . . . ." Ex. O ('089 App. – 2/28/01 A't at 9 (emphasis added)). In this amendment, Affymetrix explicitly stated that the "encoding system" carried by each substrate such as a bead is a ***different*** entity than the reagent (which is the "binding polymer" of the '432 patent claims).[6]

During a subsequent interview with the examiner, Affymetrix discussed "[c]hanges to the claims ***to clarify [the] distinction between the encoding system and the reagent as a binding reagent.***" Ex. P ('089 App. – 9/20/01 Interview Summary). The representations and amendments Affymetrix made before the Patent Office clarifying the distinction between the encoding system and the binding reagent resulted in claim allowance. Affymetrix also made it explicitly clear that the claims do not encompass encoding systems in which the binding reagent serves as the encoding system.

Consequently, Affymetrix's proposed construction should be rejected for encompassing encoding systems that are not distinct entities from the binding polymer attached to the substrate bead. The law is explicit that Affymetrix's disclaimer requires adoption of a claim construction excluding such encoding systems even if, as Affymetrix wrongly contends, such an interpretation excludes some of the embodiments. *Rheox, Inc.*, 276 F.3d at 1326-27. It is Affymetrix that violates basic principles of claim construction by attempting to capture claim scope through an overbroad claim construction covering subject matter explicitly excluded during patent prosecution. *See Southwall Techs., Inc.*, 54 F.3d at 1576.

In contrast to Affymetrix's overbroad definition, Illumina's proposed construction is the only interpretation consistent with the entire intrinsic record.[7] The plain language of the claim requires that

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[6] U.S. Application No. 09/362,089 shares the same specification as its continuation, the '432 patent. The '432 patent specification identifies reagents as binding polymers in that the reagents are "capable of interacting with their specific targets while attached to the substrate." '432 col. 6:33-35; *see also id.* at col. 6:28-30 ("The present invention relies in part on the ability to synthesize or ***attach specific recognition reagents*** at known locations ***on a substrate*** . . . ." (emphasis added)) .

[7] *See* Illumina Op. Br. at 16-18. In addition, Affymetrix's reliance on the extrinsic and out-of-context testimony of two deponents formerly associated with Illumina regarding "encoding," and an Illumina publication using the term "decoding," is unfounded as such "evidence" is in the abstract, divorced from the intrinsic record. *See Phillips*, 415

the binding polymers are attached to beads, which have been coded with an "encoding system," excluding the circumstance where the binding polymers are the encoding system. Further, as explained above and in Illumina's opening brief, Affymetrix confirmed this understanding that the "encoding system" is a separate, distinct entity from the binding reagent during exchanges with the Patent Office. *See* Illumina Op. Br. at 16-17.

Finally, the specification is also in agreement. Affymetrix points to a specification discussion of coding information on molecules such as nucleic acids, but this discussion never mentions beads or binding polymers at all. *See* '432 col. 58:11-40 (identifying use of a molecule, such as a nucleic acid, as a marker for providing information like manufacturer, date, source, manufacturing details, or origin). To the extent this discussion is relevant at all, it supports Illumina's proposed construction that the "encoding system" is a separate entity from the binding reagent because in every example the markers are clearly separate entities from the drug, chemical sample, organic compounds, food, or toxic waste being encoded. *See id.* Similarly, each of the bead-related encoding systems contemplated by Affymetrix — magnetic, shape, color, or combination — is a bead property or characteristic distinct from the probe (binding polymer) attached to the bead. *See* '432 col. 21:47-64. For all of the above reasons, Illumina's proposed construction should be adopted.

2. "target specific sequence"

Illumina's Construction	Affymetrix's Construction
a known sequence of a polymer that binds with specificity to the target at the sequence to be determined	a known polymer sequence that has affinity for another sequence

The dispute appears to be whether a "target specific sequence" is intended to bind to the sequence to be determined (***the*** "target") or to any sequence that has "affinity" for a target specific sequence. Illumina's definition is based on the plain meaning of "target" as set forth in the patent's specification. In

F.3d at 1319 ("[E]xtrinsic evidence . . . is unlikely to result in a reliable interpretation of patent claim scope unless considered in the context of the intrinsic evidence.").

contrast, Affymetrix's construction is overbroad in that it covers any polymer with "affinity" to another sequence regardless of whether the bound sequence is the intended one or not.

As an initial matter, Affymetrix's construction seeks to read the term "target" right out of the claim. Affymetrix's construction requires just a sequence specific to ***something***, not a target. But the claim reads "***target*** specific sequence," not "***anything at all*** specific sequence" or "***tag*** specific sequence." The claim language itself thus defeats Affymetrix's construction. *See Apple Computer*, 234 F.3d at 25.

The claim language and the specification describe a "target specific sequence" in the context of a known "sequence specific recognition reagent" attached to the substrate, intended to bind with a "target" molecule to be analyzed for sequencing, fingerprinting, or mapping. '432 cols. 2:29-33; 6:28-61 (Overall Description) (describing "target specific sequences" as "sequence specific reagents" on a substrate that react with specific targets); *see also* Illumina Op. Br. at 19-20. Affymetrix's example of "tag" sequences, in contrast, only appears in the specification in the context of ***preparing a substrate***, a process separate from the analysis of the target sample for sequencing, fingerprinting, or mapping. '432 cols. 27:10-67 (appearing in section entitled "B. Preparation of Substrate Matrix"); 33:66-34:22 (discussing the "tag" sequences method as a better alternative for attaching the binding polymer to the substrate). In particular, the specification discusses the use of such "tag" sequences for positionally attaching known probe sequences on the substrate in order to identify the probe sequence ***prior to*** target sequence analysis. '432 cols. 27:37-43; 34:3-10. The actual description of "tag" sequences itself confirms that they are separate from and not to be confused with "target specific sequences."

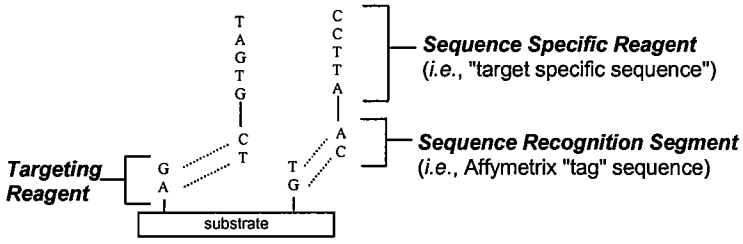
Indeed, "tag" sequences are defined differently than "target sequences" in the specification, precluding Affymetrix's argument that such sequences are "targets." Affy. Op. Br. at 14.[8] Specifically, the patent describes a short oligonucleotide on the substrate called a "targeting reagent" used to attach "sequence specific reagents" (*i.e.*, the "target specific sequence") at specific locations on a substrate:

[8] Affymetrix again cites unrelated patents-in-suit to argue an overbroad definition of "target" that is irrelevant to the asserted claim term at issue. *See* Affy. Op. Br. at 13 n.6.

> [A] relatively short specific oligonucleotide is used which serves as a ***targeting reagent*** for positionally directing the ***sequence recognition reagent***. For example, the sequence specific reagents ***having a separate additional sequence recognition segment*** (usually of a ***different polymer from the target sequence***) can be directed to target oligonucleotides attached to the substrate.

'432 col. 27:37-43 (emphasis added).[9] As depicted in the explanatory figure below, these "sequence specific reagents" each contain a "separate additional ***sequence recognition segment***," which Affymetrix calls the "tag" sequence, that binds to the "targeting reagent" on the substrate.

Method to Prepare a Substrate Using "Targeting Reagents"



The description explicitly states that the "sequence recognition segment" is a "***different polymer from the target sequence***." *Id.* (emphasis added). By distinguishing the "sequence recognition segment" (Affymetrix's "tag" sequence) from a "target sequence," the specification expressly rejects that such "tag" sequences could be "targets." In fact, the concept of "tag" sequences never appears in any of the specification's discussion of "target sequences" or "target nucleotides." *See, e.g.*, '432 col. 28:1-17. Consequently, Affymetrix's "tag" sequences example rebuts its own argument that the "target" could be a sequence other than the one to be analyzed.

In contrast, Illumina's construction is fully supported throughout the specification. For example, the specification explains that the "target specific sequence" is specific to the target polymer to be analyzed for sequencing, fingerprinting, mapping, or other screening applications. '432 cols. 2:29-33; 6:28-61 (Overall Description) (describing "target specific sequences" as "sequence specific reagents" on a

[9] "Target" is used as a verb in this context, "***to*** target," in contrast to the noun "target specific sequence" of the asserted claims. *See* '432 col. 82:4-8 (using "target" as a verb in the context of positionally locating clones for mapping).

substrate that react with specific targets); 7:25-41 (referring to the mapping of a "target molecule of interest").

Indeed, the sequencing application example Affymetrix cites further proves Illumina's argument. In this sequencing application, the claimed invention is used to determine the sequential order of the nucleotides in an unknown DNA sample. '432 cols. 7:11-14; 9:43-45. Here, the collection of "target specific sequences" include most, if not all, possible combinations of sequences of a particular length in order to analyze the unknown "target." '432 col. 22:6-23. The "target specific sequences" hybridize to subsequences within the "target" DNA sample to determine the target's entire sequence. '432 col. 22:24-25; *see also* '432 cols. 6:54-67 (describing how "sequence specific recognition reagents" hybridize "with specificity to subsequences found on the target sequence" to derive the entire target sequence); 7:11-23 (referring to the hybridization of the target sequence for fingerprinting and mapping). This sequencing example, and others throughout the specification, confirm Illumina's construction that the "target specific sequence" is a known polymer sequence that binds to the sequence to be analyzed. *See Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998) ("The construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction.").

III. THE CHIP PATENTS

A. The '531 Patent

1. "probe array"

Illumina's Construction	Affymetrix's Construction
a collection of probes, at least two of which are different, that are surface-immobilized (chemically-linked) to a single surface	a collection of surface-immobilized molecules, at least two of which are different, that can be recognized by a particular target

The parties appear to agree that the construction of "probe array" must include a collection of surface-immobilized probes, at least two of which are different. The dispute before the Court is whether to allow Affymetrix to broaden the claims well beyond what is described in the patent, given the intrinsic

evidence clarifying that the probes constituting a probe array must be chemically linked to the same single surface.

As an initial matter, Affymetrix's construction should be rejected as inconsistent with the explicit language of the asserted claims, which require that the probes in the array are on a single surface of one wafer. *See* '531 claims 1-4 ("***a wafer*** comprising ***on its surface*** a plurality of probe arrays" (emphasis added)).

The overbreadth of Affymetrix's proposed construction is further demonstrated by the '531 specification. Affymetrix relies on a single passage about substrates in the specification in an attempt to prove the "possibility of more than a single surface," but this reliance is misplaced because Affymetrix selectively quotes this discussion, implying a non-existent relationship between probe location and substrate surfaces. *See* '531 col. 9:29-45. The entire passage contains two paragraphs. The first paragraph discusses the substrate and various alternative surface configurations and states that the probes in an array "sample" are formed on the single surface of the substrate.

> The substrate is preferably flat but may take on a variety of alternative surface configurations. For example, the substrate may contain raised or depressed regions on which the probes are located. ***The substrate and its surface preferably form a rigid support on which the sample can be formed***. The substrate and its surface are also chosen to provide appropriate light-absorbing characteristics. . . . Other substrate materials will be readily apparent to those of skill in the art upon review of this disclosure. In a preferred embodiment, the substrate is flat glass or silica.

'531 col. 9:29-36 (emphasis added).

The second paragraph of the "substrate" discussion relates to the composition of the surfaces of the substrate and says nothing about probes.

> Surfaces on the solid substrate usually, though not always, are composed of the same material as the substrate. Thus, the surface may be composed of any of a wide variety of materials, for example, polymers, plastics, resins, polysaccharides, silica or silica-based materials, carbon, metals, inorganic glasses, membranes, or any of the above-listed substrate materials.

'531 col. 9:44-50. While it is true that any three-dimensional object such as a substrate has more than one surface, this discussion is limited to whether the surfaces of a substrate can consist of the same or different material from that of the substrate, and nothing more.

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The lack of any evidence supporting Affymetrix's assertion that the '531 invention is not limited to chemically linking probes to a single surface further exposes the overbreadth of Affymetrix's proposed construction. For example, Affymetrix argues that the specification discusses "attaching probes to, for example, a membrane or a resin, which is then in turn attached to the underlying support," but the cited specification support merely identifies membranes as a type of substrate surface and says nothing about probe attachment. *See* '531 col. 9:44-50. Ultimately, regardless of whether the substrate surface is composed of the same material or something different (such as a membrane), the '531 specification only contains one discussion of how to "immobilize" the probes in an array, by attaching the probes through chemical linkage to a single substrate surface using either VLSIPS™ or other *in situ* synthetic techniques. *See* '531 cols. 9:11-10:17. Likewise, Figure 8 of the '531 patent provides the only depiction of probe immobilization, and that requires chemical linkage of the probes to a single surface of a substrate.

Aside from this discussion in specification columns 9 to 10, and the drawing of figure 8, no other description of how to "immobilize" the probes exists in the '531 specification. Thus, contrary to Affymetrix's contention, the inventors did limit their invention through their narrow disclosure, which focuses on "light-directed probe synthesis" and mentions one alternative synthesis by chemical techniques to the exclusion of any other undescribed, unmentioned, alleged "ways to immobilize probes." *See Aquatex*, 419 F.3d at 1381-82 (Fed. Cir. 2005) (limiting disputed term "fiberfill batting material" to synthetic or polyester fiber composition as described to the exclusion of natural fibers in the intrinsic

record); *Watts*, 232 F.3d at 883 (limiting the disputed term to the only method described in the specification regardless of whether one of ordinary skill would be aware of other methods because, *inter alia*, the specification failed to discuss an embodiment using any other method).

Contrary to Affymetrix's contention, Illumina's proposed construction defines "probe array" consistent with the individual definitions of "probe" and "array" in light of the specification and the prosecution history, which uniformly agree that the probes are immobilized through chemical linkage to the single surface of a substrate wafer. *See* Illumina Op. Br. at 22-24. As discussed, the claims themselves require that the probes in the array are on a single surface of one wafer, and the only discussion in the '531 specification of how to "immobilize" the probes in an array is to a single surface through direct synthesis of the probes onto the substrate, which requires chemical linkage of the probes to that single substrate surface. *See, e.g.*, '531 cols. 9:11-10:17; Fig. 8. Furthermore, in every embodiment of the '531 patent, every probe in a probe array is immobilized on a single surface. *See, e.g.*, '531 cols. 8:1-5, 8:23-31; Figs. 4, 5; *see also* '531 cols. 7:57-67, 8:22-26; Figs. 3, 6, 7. Moreover, in order to obtain allowance of the asserted claims, Affymetrix authorized an examiner amendment conforming the claims to require all of the probe arrays be on a single surface of a single wafer as well. *See* Illumina Op. Br. at 23-24 (citing relevant prosecution history). The intrinsic record confirms that at least the probes of each probe array (if not all probe arrays) must be immobilized through chemical linkage on a single surface.

2. "arranged in a spacially defined and physically addressable manner"

Illumina's Construction	Affymetrix's Construction
each probe in an array is placed in a different pre-determined location on the surface	located in a particular location and capable of being accessed

The dispute before the Court is whether the probes in an array must be "arranged," *i.e.*, "placed" in pre-defined positions on the surface of the wafer or if the probes need not be arranged in the claimed array at all. Affymetrix's proposed construction is fundamentally flawed because it ignores the claim requirement that the probes be "arranged." In contrast, Illumina's proposed construction reflects the claim language and the '531 specification's consistent descriptions that each probe is selected and assigned a

specific location in an array depending on contemplated use, as confirmed by the required amendment of the '531 claims made by the Examiner.

Affymetrix's proposed construction reads out the explicit claim requirement that the probes be "arranged" in the array. Even though Affymetrix cannot contest that "arranged" has no special meaning in the intrinsic record and that the plain meaning of "arranged" dictates specific placement or ordering of the probes in the array, Affymetrix nonsensically argues that the probes need not be arranged in the array so long as each probe's location on the array may be determined post-experiment. Beyond the fact that Affymetrix's construction fails to give meaning to "arranged," it further would render the whole limitation "arranged in a spacially defined and physically addressable manner" meaningless. A probe array is only an "array" if its probes are located in a particular location and capable of being accessed -- that is what a probe array is. The inclusion of the additional limitation "arranged in a spacially defined and physically addressable manner" has to mean more than that. *See Wright Med. Tech.*, 122 F.3d at 1444 (rejecting construction that would render claim term to be surplusage). Indeed, this language was specifically required to be added by the Examiner to clarify that the probes in the array must be "arranged" in an orderly fashion. *Compare* Ex. X (App. No. 08/476,850 Original Claims 65, 67 at 30) *with* Ex. Y (App. No. 08/476,850 – 3/25/96 Notice of Allowability at 2).

Contrary to Affymetrix's argument, the claim language itself and the specification explicitly express when the specific location of each probe is determined -- prior to formation of the biological chip plate. The asserted claims involve "a method for making a biological chip plate" using a wafer whose surface contains more than one probe array, where the probes are ***already*** "arranged," in a "spacially defined and physically addressable manner." *See* '531 claims 1-4. Use of the past tense of "arrange" confirms that the probes have previously been placed in a spacially defined and physically addressable manner on the wafer surface. Likewise, the specification explicitly discusses selecting probe content and arrangement of these probes in the array in the past tense -- "probes ***arranged*** in arrays, each probe ***assigned*** a specific location." *See, e.g.*, '531 col. 1:15-16 (emphasis added). Thus, the express language of the claims and the specification state that the specific location of each probe is pre-determined, that is,

the probes are organized in an array by selecting and assigning each probe a specific location in the array depending on contemplated use. *See, e.g.*, '531 cols. 10:45-47, 1:15-16, 10:36-44; *see also id.* cols. 2:64-67, 8:61-9:1, 11:58-64; *see also Laitram*, 143 F.3d at 1463 (limiting disputed term to flat "driving surfaces" because nothing in the specification suggested that the driving surfaces could be anything but flat).

B. The '365 Patent

1. "housing"

Illumina's Construction	Affymetrix's Construction
casing that separates the probe array from the atmosphere	a structure in which something is contained

The issue for the Court is whether to ignore the definition dictated by the intrinsic evidence in favor of Affymetrix's dictionary-derived definition for the term "housing." Affymetrix seeks to capitalize on the fact that the term "housing" does not appear at all in the specification of the '365 patent, and thus tries to justify reliance on extrinsic evidence to fill this vacuum. But to do this, Affymetrix must ignore the testimony of its own inventor and the context of the '365 patent that clearly dictate that the term "housing" in the claims should be construed consistently with the word "casing," which is used throughout the specification. The intrinsic discussion of the term "casing" informs the claim construction analysis for the term "housing" and dictates that Illumina's proposed construction is correct.

Affymetrix seeks to rely on an extrinsic definition of the word "housing," contending that this term has a "widely-accepted meaning." Affy. Op. Br. at 28. This is wrong on several levels. First, Affymetrix simply cherry-picks the dictionary definition it likes and ignores the others that support Illumina's construction. Indeed, the next entry in Affymetrix's own dictionary citation for "housing" is "a ***fully enclosed case*** and support for a mechanism," and "casing" is listed as the second synonym for "housing" at the end of the dictionary entry. *See* Affy. Op. Br. Ex. 16 (emphasis added). Second, Affymetrix's proposed construction of "a structure in which something is contained" is actually quite a bit different from its supposed dictionary support of "anything that covers or protects" -- this definition

supports Illumina's construction just as much as Affymetrix's. One need only think of cereal "contained" in a bowl to realize that "contain" is not synonymous with "cover" or "protect" as Affymetrix argues. Third, Illumina has already cited other dictionary definitions that support the intrinsic evidence and the definition of "housing" as a "casing" that separates the probe array from the atmosphere. *See* Illumina Op. Br. at 26. This is simply not a situation in which a "readily apparent" or "widely accepted" dictionary definition can control the claim construction analysis and trump the intrinsic evidence. *Phillips*, 415 F.3d at 1319 (extrinsic evidence, including dictionary definitions, are "unlikely to result in a reliable interpretation of patent claim scope unless considered in the context of the intrinsic evidence").

This Court must properly look to the intrinsic evidence, including the '365 patent specification and prosecution history, to inform the construction of the term "housing." The embodiments in the patent show a casing that separates the probe array from the atmosphere. *See, e.g.* '365 Figures 4 & 5. The ***Summary of the Invention*** speaks of "forming a ***sealed*** thermostatically controlled chamber" in "some embodiments," and for the "other embodiments" refers to "sealing means" for the package. '365 cols. 2:2; 8-9; 11; 14-15 (emphasis added). The Federal Circuit has recognized that patent specification statements of overall applicability, such as in the Summary of the Invention, are generally more persuasive than descriptions of a particular embodiment with respect to claim construction. *See C.R. Bard, Inc.*, 388 F.3d at 864.

Affymetrix also ignores its prosecution history statements distinguishing prior art that now would be covered by its litigation-driven claim construction. Affymetrix distinguished the Mitsuhashi reference during prosecution as not teaching "a housing including a fluid cavity for hybridization." Ex. CC (App. No. 09/907,196 – 12/20/01 A't at 14). But Mitsuhashi teaches a microtiter plate with wells (and optionally beads) that contain biological polymers for hybridization -- most clearly the wells are "structures in which something is contained." Ex. KK (U.S. Patent No. 5,639,612 ("Mitsuhashi") at cols. 4:6-12; 7:35-48; 18:16-23). This Court must reject Affymetrix's proposed construction as directly inconsistent with the position it took during prosecution to get around the prior art. *Spectrum Int'l*, 164 F.3d at 1378 (claims may not be construed one way during prosecution and another in litigation).

Having nothing else to support its construction, Affymetrix finally posits several rhetorical questions about Illumina's proposed construction to suggest that the jury would not be able to apply the construction. But it is Affymetrix's construction of "a structure in which something is contained" that begs more questions than it answers, notably what does it mean for something to be "contained"? Affymetrix's criticism of Illumina's construction does not highlight any significant ambiguities and, in reality, is just an indictment of the choice of Affymetrix's patent counsel to use claim terms that appear nowhere in the specification. The objective of claim construction is to find language that a jury can apply that reflects the proper meaning of the claims to one of ordinary skill in the art. Illumina's proposed construction satisfies this objective, while Affymetrix's changes the meaning of the claim and should be rejected.

This Court should follow the intrinsic evidence, as confirmed by one of Affymetrix's own inventors of the '365 patent, and adopt Illumina's construction of the term "housing": casing that separates the probe array from the atmosphere.

2. "biological polymers immobilized on a surface/substrate"

Illumina's Construction	Affymetrix's Construction
two or more biological polymers of different sequence chemically linked to a single surface	two or more surface-immobilized biological polymers that are recognized by a particular target

As set forth in Illumina's opening brief, the two sub-issues presented by this claim construction dispute are (1) what is meant by the term "immobilized," and (2) whether the polymers must be bound to a single surface or substrate. Affymetrix's proposed construction ducks these issues and instead invites the Court to have the jury (mis)apply its lay understanding of the terms to result in a gross distortion of the claim scope and the invention disclosed in the patent.

Affymetrix first ducks the issue of "immobilization," ignoring the fact that this term is understood by those of skill in the art as requiring chemical linkage of the polymers to a surface.[10] Affymetrix has

[10] Even Affymetrix is on record that "immobilization" requires covalent (*i.e.* chemical) linkage in this context. In a filing with the European Patent Office opposing OGT's European patent, Affymetrix argued that a prior art reference

nothing to say about the extensive discussion of chemical linking in the specification. *See* Illumina Op. Br. at 28. Affymetrix also does not specifically point to any other way of "immobilizing" a polymer on a surface other than by chemical linking. All Affymetrix can do is point out that the claim does not expressly use the term "chemically linking" -- of course it does not, but it does use a term that one of ordinary skill in the art would consider synonymous. While Affymetrix pretends that there are "other" ways to immobilize polymers, it cannot explain what these are or how they would work, let alone point to their disclosure in the '365 patent. What is disclosed is Affymetrix's core technology of "Very Large Scale ***Immobilized Polymer*** Synthesis" (*see* '432 col. 7 for explanation of VLSIPS™) and a discussion of how this technology involves the use of chemically linking the polymer to a surface. '365 cols. 4:47-5:6.

Affymetrix also attempts to distort one paragraph of the specification, and ignores the rest, when it argues that the claims cover more than a probe array immobilized on a single surface. As the totality of its intrinsic support, Affymetrix cites one passage from the specification that refers to "a wafer" with "probe arrays" (plural) that can be composed of a variety of materials. *See* Affy. Op. Br. at 27. This passage, however, says ***nothing*** about having a ***single probe array*** on more than one surface. Indeed, the specification explains that this "wafer" can then be diced up into separate "chips" that each contain a single probe array, and then these chips are packaged according to the invention set forth in the patent. '365 cols. 6-8. There is no support for Affymetrix's proposed construction that permits probes from a single probe array to be on more than one surface.

The intrinsic evidence in fact dictates Illumina's proposed construction. *See* Illumina Op. Br. at 29. And as discussed in Illumina's opening brief, the ***only*** specification support for the density limitations in the asserted claims is discussed as a "single substrate" supporting 100 different monomer sequences. '365 col. 5:45-49.[11] There is no reference to multiple surfaces or substrates having 100 different polymer

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taught that it "is well known that noncovalent immobilization of an oligonucleotide is ineffective on a solid support." Ex. LL (European Patent No. 0 373 203 – 5/31/95 Opp'n at 22). Thus, "immobilization" in the context of putting polymers on a solid support requires chemical linkage.

[11] The dependent claims that require other minimum numbers of polymers (*e.g.* claim 22 requiring 1000 different nucleic acids) are similarly only supported by the disclosure in the specification relating to "a single substrate."

sequences. Thus, this Court must construe the claims in light of the specification and the claim language to require that two or more biological polymers be chemically linked to a single support. *See Nystrom*, 424 F.3d at 1144-45 (claim constructions must not be divorced from the context of the written description).

IV. THE SOFTWARE PATENT

A. The '716 Patent

Like its arguments for the other patents and claim terms, Affymetrix's arguments for its proposed constructions for the '716 patent are notably deficient in their citations to the evidence the Federal Circuit deems most persuasive -- the claims, the specification, and the prosecution history. Affymetrix's aversion for the intrinsic evidence is its only option -- it is the only way Affymetrix can seek to contort the claims of the '716 patent to come close to encompassing Illumina's products.

1. "probe"

Illumina's Construction	Affymetrix's Construction
a nucleic acid of known sequence that is capable of hybridizing to a complementary sequence of the unknown sample nucleic acid	a nucleic acid of known sequence that is capable of hybridizing to its complementary sequence

Affymetrix acknowledges that the parties' proposed constructions are similar, and that the issue boils down to whether the complementary sequence is from "the unknown sample nucleic acid." Affymetrix does not suggest that Illumina's proposal of this additional language is wrong or inconsistent with the intrinsic evidence, but instead contends that this language is "redundant" to other language in the claim. But if redundancy is Affymetrix's only objection to Illumina's proposed construction, why is there a dispute? The answer is that Affymetrix wants to later use its ambiguous construction to read the limitation on "tag"-based technology that it distinguished to get the claims in the first place.

The claims of the '716 patent themselves dictate that Illumina's construction is the correct one. As Affymetrix points out, the claims require hybridization of the probe with "said sample sequence." '716 col. 41:67. The antecedent basis for the term "said sample sequence" comes from the preamble and its reference to "an unknown base in a sample nucleic acid sequence." *Id.* at col. 41:61. Illumina's

construction simply incorporates this antecedent basis into the body of the claim to eliminate any confusion as to what the probe is hybridizing with -- an unknown sample nucleic acid. *See Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1356-57 (Fed. Cir. 1999) (noting the importance of an antecedent basis in claim construction).

As discussed in Illumina's Opening Brief, Affymetrix puts forth an ambiguous claim construction for the term "probe" in order to set up an attempt to read the claims back on the prior art that was distinguished during prosecution. Affymetrix specifically distinguished prior art during prosecution that "uses a single probe which will hybridize to a ***tag*** on the nucleic acid ladder fragments," as contrasted with the '716 patent's "probe intensities that indicate the extent of hybridization of probes differing by a single base and the ***sample*** nucleic acid sequence." Ex. DD (App. No. 08/327,525 ("'525 App.") – 5/20/96 A't at 13-14). Thus, the Court should adopt Illumina's construction including the phrase "of the unknown sample nucleic acid" to ensure the jury is not confused or misled into applying the claim against tag-based or any other hybridizations that do not involve the unknown biological sample of interest.

2. "probe intensity"

Illumina's Construction	Affymetrix's Construction
intensity from a labeled sample nucleic acid hybridized to a probe location	a detectable signal, *e.g.*, fluorescence

The dispute for the term "probe intensity" seemingly distills into two issues: (1) whether the term should be construed consistently with the intrinsic evidence to require an intensity from a labeled sample nucleic acid, and (2) whether the intensity must be associated with a particular probe location. Affymetrix's proposed construction simply ignores the language of the term "***probe*** intensity" and the whole concept of how this is generated and used as described in the '716 patent.

As for the first issue, Affymetrix does not dispute that ***all*** of the intrinsic evidence depicts the "probe intensities" as emanating from a labeled sample nucleic acid. Despite the disclosure of only one way in the intrinsic evidence, Affymetrix now argues that there are "many ways for a 'probe intensity' to indicate that the probe has hybridized." Affy. Op. Br. at 32. Affymetrix has only attorney argument, not

evidence, to support this contention. At bottom, Affymetrix wants to morph this term into merely any "intensity" that is not tethered in any way to the intrinsic evidence or the whole thrust of the invention. Affymetrix's construction reads "probe" out of the term "probe intensity" and must be rejected. *See Apple Computer*, 234 F.3d at 25.

The Federal Circuit in *Phillips* recently reaffirmed its longstanding guidance that "the specification 'is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term.'" *Phillips*, 415 F.3d at 1315 (*quoting Vitronics*, 90 F.3d at 1582). Affymetrix invites the Court to completely ignore this "single best guide" when construing the term "probe intensity." While Affymetrix predictably accuses Illumina of seeking to import a claim limitation, it cannot justify its proposed construction, other than to say there is "nothing to exclude" its construction. But this argument seeks to turn the case law on its head -- contrary to Affymetrix's view, it "is not entitled to a claim construction divorced from the context of the written description and prosecution history." *Nystrom*, 424 F.3d at 1144-45.

Affymetrix also ignores the intrinsic evidence, and the basic underlying science, when it contends that "probe intensity" need not emanate from a particular probe location. Again, Affymetrix does not dispute that the entirety of the intrinsic evidence supports Illumina's construction requiring a "location" for the intensity, and resorts to attorney argument for its only support for "other" ways to have a probe intensity without a location. But even Affymetrix's examples must have locations -- *e.g.,* on a specific support, inside a specific column, in a specific beaker -- in order for any kind of experiment to be run. The specification clearly explains that base sequence can only be called "since the monomer sequence of the polymers on the substrate ***is known as a function of position***." '716 col. 4:46-47 (emphasis added); *see also* cols. 1:47 (intensity "indicating the ***locations*** where the labeled nucleic acids bound to the chip") (emphasis added); 4:38-39 ("detect the ***locations*** where labeled receptor (*) has bound to the substrate") (emphasis added).

Affymetrix then tries, but fails, to use the principle of claim differentiation to attack a locational requirement for the probe intensity. Affymetrix's argument relies on the false premise that the only way

the probe intensities can be associated with corresponding locations is for the probes to be arranged in an array format, as is expressly required by claim 9. This premise is incorrect -- probes and their corresponding intensities can have locations without being arrayed on a single substrate, although this is the only way described in the patent. They could, for example, be located on separate substrates, not in an array. But Affymetrix cannot explain -- because it makes no sense -- how the invention can possibly work if the probe intensities are not associated with a particular location. The only way sequence information is derived is by knowing the particular probe that is located at a particular location, so that when a probe intensity is detected at that location, information about the unknown sample nucleic acid can be determined. This was confirmed by the applicants during prosecution, in which they refer to the fact that the ***locations*** of the probes are known as a way to distinguish the '716 patent claims over the prior art:

> In the present invention, the ***locations of the hybridized probes are known*** and, as such, the computer algorithms of Weiss and Stockham would indeed seem to teach away from the present invention which is directed to calling an unknown base according to ***the probe intensities from nucleic acid probes*** that differ by a single base.

Ex. DD ('525 App. – 5/20/96 A't at 14 (emphasis added)). Illumina's construction, unlike Affymetrix's, is consistent with the intrinsic evidence (and common sense) and must be adopted.

3. "corresponding to probe intensities for a plurality of nucleic acid probes"

Illumina's Construction	Affymetrix's Construction
two or more probe locations each having one and only one probe intensity	relating to a detectable signal, *e.g.*, fluorescence, from two or more nucleic acid sequences of known sequence that are capable of hybridizing to a complementary sequence

The two disputes with respect to this claim term relate to (1) whether an intensity is associated with a location, and (2) whether each probe location can have more than one intensity. With respect to the first issue, Affymetrix relies on the same evidence-free argument as to how an intensity need not be associated with a particular location, and these arguments fail for the same reasons discussed above. On the second issue, Affymetrix actually cites to one piece of intrinsic evidence to try to support its

argument, but ignores the remainder of the intrinsic evidence that makes clear that each probe location can have only a single probe intensity.

Affymetrix seeks to rely on discussion in the '716 specification of a specific concept referred to as "Pooling Processing" to try to justify that a particular probe location can have more than one intensity associated with it. The discussion of "Pooling Processing" relates to the concept of labeling a reference and a sample nucleic acid with two different markers, and then processing the reference and sample together. *See generally* '716 cols. 21:35-22:21. But the prosecution history makes very clear that this "Pooling Processing" discussion has nothing at all to do with the claims of the '716 patent, and cannot trump the clear statements during prosecution that the claims do not cover probes having more than one intensity.

The prosecution history shows that the claims that issued in the '716 patent ***do not*** relate to the "Pooling Processing" concept on which Affymetrix now seeks to rely. In the original patent application, Affymetrix included claims in three groupings -- CallSeq™, ViewSeq™, and Pooling Processing. Ex. MM ('525 App. – 10/21/94 Patent App. at 45-50). Under each of these headings, Affymetrix included specific claims relating to these separate embodiments described in the specification. Under the "Pooling Processing" heading, Affymetrix included application claims 21-26 that referred to labeling one nucleic acid with a "first marker" and a second nucleic acid with a "second marker." *Id.* at 47. The claims relating to probe intensities and comparison of probe intensities to call an unknown base, were included under the CallSeq™ heading. *Id.* at 45.

In the first office action, the Examiner issued a Election/Restriction Requirement, finding that each of the three groupings disclosed a distinct invention, and requiring Affymetrix to elect one of the groupings on which to proceed with prosecution in the instant application. Ex. NN ('525 App. – 9/19/95 Office Action at 2-3). In response to this Restriction/Election Requirement, Affymetrix then cancelled all of the claims relating to the ViewSeq™ and Pooling Processing inventions, and proceeded with prosecution only on the claims relating to the CallSeq™ invention. Ex. OO ('525 App. – 10/23/95 Resp.

to Restriction Req't). In compliance with this Restriction/Election Requirement, no claims relating to the Pooling Processing invention were ever reintroduced into the application that became the '716 patent.

In the correspondence that immediately followed Affymetrix's decision not to pursue the Pooling Processing claims in the application that led to the '716 patent, Affymetrix then clarified that the remaining claims were not intended to cover any multi-intensity embodiment. In an Office Action dated December 19, 1995, the Examiner raised two questions asking how a single probe could generate more than one intensity:

> Further the recitation of "each probe intensity of a probe" because ***it is unclear how a single probe can have more than one intensity*** (as implied by the use of the term "each").
>
> * * *
>
> Claims 13 and 14 are indefinite in reciting "Probe intensities of a probe" in that ***it is not clear how "a" probe generates more than one intensity.***

Ex. FF ('525 App. – 12/19/95 Office Action at 3-4 (emphasis added)). Affymetrix's response is telling – it did not explain that a single probe could have more than one intensity, but instead amended the claims to clarify that multiple "probes" each have their own "probe intensities":

> Also, the Examiner stated that "each probe intensity of a probe" is unclear. Claim 67 recites instead "each probe intensity of probes" (emphasis supplied). Accordingly, the rejection does not apply to the new claims.
>
> * * *
>
> In regard to claims 13 and 14, the Examiner stated that it is not clear how "a" probe generates more than one intensity. Claims 73 and 74 instead contain the plural "probes."

Ex. DD ('525 App. – 5/20/96 A't at 11). The prosecution history thus confirms that the claims that survived the restriction and election are to be construed such that each "probe" has a single probe intensity associated with it.

No one of ordinary skill reading the intrinsic evidence, including this exchange in the prosecution history, could conclude that the claimed "probes" could each have more than a single associated probe intensity as argued by Affymetrix. **REDACTED**

REDACTED

Affymetrix cannot run away from its prosecution history admissions now -- the claims must be construed to require "two or more probe locations each having one and only one probe intensity."

4. "indicating an extent of hybridization"

Illumina's Construction	Affymetrix's Construction
indicating the strength of binding so as to distinguish a single-base mismatch	relating to the relative binding of

The dispute with respect to this claim term is two-fold: (1) whether the term should be construed to reference the "strength" of binding, and (2) whether the binding must distinguish single base mismatches. Once again, Affymetrix's construction flip-flops the case law, elevating a dictionary definition over the intrinsic evidence. Illumina's construction, in contrast, comes straight from the intrinsic evidence.

Both parties agree that the concept of an "extent of hybridization" refers to binding, but disagree as to whether it must indicate a strength of binding. As cited in Illumina's opening brief, the '716 specification refers to the fact that the highest probe intensity indicates the sample nucleic acid has "bound ***more strongly***" to the probe. '716 col. 4:43-45 (emphasis added); col. 7:59-62 ("the intensity should be highest for the probe that binds ***most strongly*** to the sample sequence" (emphasis added)). Affymetrix's construction ignores the references to the "strength" of binding and must be rejected.

Affymetrix also ignores the clear intrinsic evidence requiring that the intensities must "indicate the extent of hybridization" so as to distinguish single base mismatches from one another. The '716 patent specification includes multiple examples that all require discrimination of the probe intensities of probes that differ by a single base. *See* '716 cols. 7:55-58; 11:4-7; 11:11-13. Moreover, Affymetrix distinguished its claimed invention during prosecution because its "probe intensities indicate an extent of hybridization of probes ***differing by a single base.***"[12] Ex. DD at 13; Ex. GG ('525 App. – 7/9/96 Office Action at 5 (emphasis added)).

Affymetrix finally argues that "[t]he phrase 'indicating an extent of hybridization' says nothing about the purpose of the indication or what the indication will be used for." Affy. Op. Br. at 36. This is wrong. The claims of the patent very clearly describe that the probe intensities indicate an extent of hybridization to allow a base call to be made. In the examples discussed in the specification, each of the probes only differ by a single base. Thus, if the probe intensities do not "indicate an extent of hybridization" so as to distinguish single base mismatches, no base call can be made. Affymetrix's construction, which would render the disclosed embodiments inoperable, must be rejected. *Talbert Fuel Sys. Patents Co. v. Unocal Corp.*, 275 F.3d 1371, 1376 (Fed. Cir. 2002), *vacated* and later *aff'd*, 347 F.3d 1355 (Fed. Cir. 2003) ("a construction that renders the claimed invention inoperable should be viewed with extreme skepticism").

5. "comparison of said plurality of probe intensities to each other"

Illumina's Construction	Affymetrix's Construction
ranking of probe intensities from a hybridization experiment	an examination of the detectable signals of two or more probes in relation to each other

The dispute on this claim term is whether a "comparison" of intensities actually requires evaluation of the intensities to rank them relative to one another, or whether some ambiguous, indefinite

[12] Specifically, Affymetrix distinguished prior art that relied in part on enzymatic reactions, in addition to hybridization, to help discriminate a perfectly matched sequence from one that had a mismatched sequence. Affymetrix now seeks to reverse field and recapture Illumina's assays that rely on enzymatic assays in order to distinguish single base mismatches.

"examination" of the intensities is enough. Affymetrix again cites as its primary evidence an extrinsic dictionary definition, and then seeks to distort the '716 specification to attack Illumina's construction.

Affymetrix's proposed construction reads the requirement of a "comparison ... of probe intensities ***to each other***" right out of the claim. The claim language, as informed by the rest of the intrinsic evidence, clearly requires this "comparison" to result in a determination that one intensity is greater than another (*i.e.*, A>B, A<B, or A=B). By necessity, this "comparison" thus ***ranks*** the intensities as is required by Illumina's construction. Affymetrix's ambiguous non-construction would essentially mean that two probe intensities, by virtue of their existence alone, would be "compared" to one another. Since the base call must be made based on this comparison, however, it follows that Illumina's construction to identify the higher (or highest) intensity is the correct one.

Affymetrix is wrong when it argues that "the specification describes comparisons ***other than*** ranking of probe intensities." Affy. Op. Br. at 37 (emphasis in original). Indeed, Affymetrix's two examples of "non-ranking" comparisons actually ***do rank*** the probe intensities -- they each identify "the highest intensity base" and then perform mathematical steps to determine if the base will be called according to this "highest intensity base" (*i.e.*, they evaluate if the highest intensity is statistically distinguishable from the others). *See* '716 cols. 8:61-9:2 ("base intensities are sorted in descending order of intensity" to identify the "highest intensity base"); *id.* at col. 12:66-67 ("highest intensity base"). There is no intrinsic evidence, or logic, to support Affymetrix's argument that two intensities can be "compar[ed] ... to each other" without identifying which one has a higher intensity (*i.e.* by ranking them).[13] And there is certainly no intrinsic support that any comparison that does not rank the intensities can be used to make a base call as is required by the claims.

Once again, Affymetrix seeks an amorphous non-construction that would allow the claim to be contorted to cover anything at all. Illumina's proposed construction, which stays true to the intrinsic evidence and is logically consistent, should be adopted.

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[13] Affymetrix is wrong that merely by taking a ratio of two numbers, without evaluating what that ratio is and indicates (*i.e.* A/B > 1, < 1, or =1), is a comparison of these numbers to each other.

6. "generates a base call"

Illumina's Construction	Affymetrix's Construction
identifies a nucleotide as A, C, G or T (or U)[14]	determines which nucleotide is most likely to be present at a particular position in a nucleic acid sequence

The parties apparently agree that a "base call" requires that a particular nucleotide (A, C, T, G or U) be called, but disagree as to whether the nucleotide is "identified" or "determined to be most likely present" at a particular position.[15] Affymetrix's construction seeks to overlay an additional, indefinite limitation that does not appear in the patent claims.

Affymetrix states flat out in its brief that "[a] 'base call' is a determination of the identity of a base, or nucleotide." Affy. Op. Br. at 38. This is precisely Illumina's definition. The parties diverge when Affymetrix seeks to further incorporate the concept that sometimes a "base call" is made with less or more confidence depending on the results of the experiment. This may be true, but it is not part of the claim term "base call." There is no reference to "confidence estimates" or "confidence codes" in the claims, and there is no basis upon which to include these concepts in the definition of "base call." Illumina's construction should be adopted.

7. "generates a base call ... according to the result of said comparison and sequences of said nucleic acid probes"

Illumina's Construction	Affymetrix's Construction
generates a base call as the base-pair complement to the probe with the highest probe intensity	This phrase should be construed consistently with Affymetrix's above proposed constructions

Affymetrix ignores the intrinsic evidence, instead relying solely on attorney argument to avoid construction of this term. Illumina's construction comes straight from the intrinsic evidence and should be adopted.

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[14] When working with RNA, the base "U" replaces "T" in the four-base code discussed above for DNA.

[15] While unnecessary and redundant, Illumina has no serious objection to Affymetrix's construction insofar as it requires that a nucleotide be determined "at a particular position in a nucleic acid sequence."

All of the examples in the '716 patent make the base call as the base-pair complement to the probe with the highest probe intensity. There is no other way described or even mentioned. Affymetrix implies that there are other ways to make the base call, but does not suggest how they would work. Moreover, Affymetrix cites back to its examples relating to other forms of "comparison," but as discussed above each of these examples all identify the "highest base intensity" (by ranking them) to call the unknown base.[16] The prosecution history further confirms that a base is "***called according to (e.g. complementary to) a base in the probe with the highest probe intensity***." Ex. HH ('525 App. – 1/13/97 A't at 14-15 (emphasis added)). This intrinsic evidence explains exactly what is meant by the claims.

At bottom, Affymetrix does not want to construe this term because it knows that any construction based on the intrinsic evidence will doom its infringement case on this patent. Affymetrix is seeking to read out the requirements that the base call be made (1) according to the results of the comparison of probe intensities ***to each other***, and (2) as the complement to the sequence of the probe. This Court should not accept Affymetrix's invitation to leave this limitation ambiguous and not provide the clarity required for the jury to properly apply this claim term to Illumina's accused products. Illumina's proposed construction requiring generation of a base call as the base-pair complement to the probe with the highest probe intensity is compelled by the intrinsic evidence and should be adopted.

[16] While some of the embodiments disclosed perform additional mathematical manipulations to assess the base call, the only decision left to be made is whether to call the base in accordance with the "highest intensity base" or to make no call at all (because the difference in intensities is not statistically significant).

CONCLUSION

For the foregoing reasons, Illumina respectfully requests that the Court construe the disputed terms of the asserted claims of the Affymetrix patents-in-suit as set forth above.

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CERTIFICATE OF SERVICE

I hereby certify that on the 18th day of April, 2006, I caused to be electronically filed the foregoing document, **PUBLIC VERSION OF ILLUMINA, INC.'S RESPONSIVE *MARKMAN BRIEF***, with the Clerk of the Court using CM/ECF which will send notification of such filing to the following:

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